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Controlling the Ir Genes

Jeremy M. Boss

By 1970, it was clear that the genes located in the MHC were key to controlling the ability to produce Abs in response to an immunogen (1, 2). Termed the immune response genes, the actual identification and sequence determination of these genes in the class II region of the human and murine MHCs occurred in the early and mid-1980s (3). By the mid-1980s, it was found that expression of the MHC class II (MHC-II) genes was regulated during the development of B lymphocytes and could be induced in many cell types by IFN-γ (4). At this time, few mammalian gene or cell type-specific transcription factors were known, and the mechanism(s) by which they functioned to recruit RNA polymerases was based mostly on in vitro system models and ignored the complexities of chromatin.

For MHC-II genes, the mechanism(s) of tissue-specific and IFN-γ regulation was a mystery. This mystery would be solved through the exploitation of novel cell lines that were created through mutagenesis and subsequent selection for the loss of MHC-II surface protein expression (5, 6). The genes deficient in these cell lines functioned in trans, suggesting that the mutant genes were trans-acting factors regulating the MHC-II genes. In addition to these cell lines, bare lymphocyte syndrome (BLS) patients were identified that expressed no MHC-II proteins on their peripheral B cells. Cell lines derived from BLS patients formed four complementation groups (A, B, C, and D), each representing a trans-acting factor responsible for MHC-II gene control (7, 8).

Conserved sequence motifs termed X and Y boxes were identified upstream of murine and human MHC-II genes (9). The definition of the conserved region was redefined ultimately to include W/Z, X1, X2, and Y box motifs. Collectively, the W-X-Y module was found upstream of all MHC-II and MHC-II-related genes (DO, DM, It, etc.). The W-X-Y module was required for IFN-γ and cell-type-specific expression (10, 11). Together with the cell lines in hand and the identification of the cis-regulatory elements, biochemistry and molecular genetics could be combined to identify the transcription factors involved.

Although the X1 box binding factor RFX and the Y box binding factor NF-Y were discovered first, these factors by themselves could not explain MHC-II cell type- and tissue-specific expression (12, 13). RFX binding activity was found in all cell types examined but was absent in BLS groups B, C, and D, suggesting that these patients had deficiencies in RFX subunits. Group A was problematic as all of the binding factors were present, but the genes were still silent. Importantly, whereas a W-X-Y box reporter gene was active in wild-type B cells, it was not active in BLS-A group cells, suggesting that the activity of this sequence was critical to the elusive factor.

Steimle et al. (14) took advantage of this information and sought to clone the missing factor by constructing a complementation cDNA library where expression of selection markers would be driven by W-X-Y box sequences. The library was used to complement Accolla’s R2.2.5 BLS-group A-like cell line. The complementing gene was named the class II transactivator or CIITA. CIITA expression explained why cells expressed MHC-II genes or not. CIITA was expressed in B cells but silenced in plasma cells (15). It was also found to be the factor induced by IFN-γ (16). It is now accepted that cells that express CIITA also express MHC-II genes. Thus, CIITA has been called the master regulator of MHC-II expression.

Today, we know that CIITA functions as a transcriptional coactivator, linking the X-Y box DNA binding factors to the transcriptional control machinery. CIITA serves as a target for multiple protein complexes, most notably histone-modifying complexes, which are necessary for activation of MHC-II promoters. CIITA is the founding member of a family of proteins thought to be involved in intracellular immune defense termed CATERPILLER, NOD, or NACHT proteins (17). CIITA itself is tightly regulated and is subject to epigenetic control as well. Although the CIITA story itself is far from complete, this month’s Pillars of Immunology article (14) solved the mysteries of MHC-II cell type-specific expression and IFN-γ control of the Ir genes.

References


